

Addition of 3-Thienyllithium to Phthalic Anhydride:  
A Simple Method for the Synthesis of  
9,10-Dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-10-one

Michal W. Majchrzak

Institute of Drug Technology, Medical Academy, Narutowicza 120A  
90145 Łódź, Poland

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Addition of 3-thienyllithium to phthalic anhydride produces a mixture of materials from which 2-(3-thienoyl)benzoic acid was easily separated. Elaboration of the acid side chain and ring closure produced the title compound in good yield.

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9,10-Dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene (**11** in Scheme I) is a promising intermediate for the synthesis of the pharmaceutical Zaditene (Ketotifene, 4-(1-methyl-4-piperidene)-9,10-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-10-one [1], since the keto functionality is already in the appropriate position. We report herein the synthesis of **11** from the acid **6** by elaboration of the carboxylic acid side chain to **10** and cyclization.

The starting acid **6** was obtained by MacDowell and Wisowaty [2] by addition of 3-thienyllithium to *o*-bromo-

benzaldehyde and subsequent reactions. The 3-thienoyl residue alternatively may be introduced *ortho* to the carbonyl function by the addition of organometallics to phthalic anhydride [3]. Thus we considered a more direct route to compound **11** using this methodology.

The addition of Grignard reagents to phthalic anhydrides has been reported [4], but similar additions of the lithium reagent are not known. Because of the ease of preparation of 3-thienyllithium (**1**), the shortest route to the adduct **3** seemed to be the addition of **1** to phthalic anhydride. The synthesis of **11** would then follow by the procedures of Scheme I.

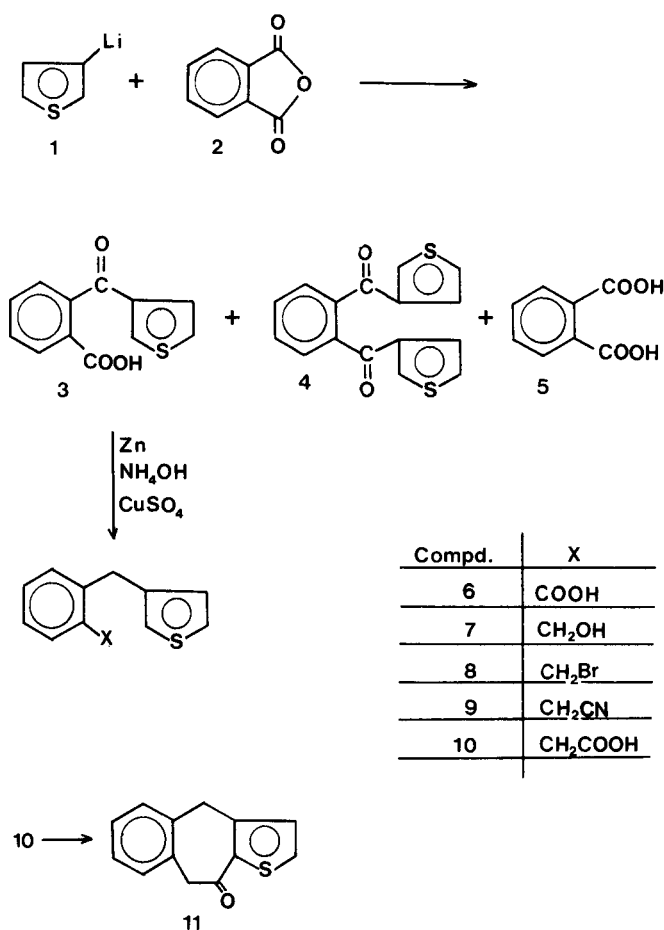
The direct addition of phthalic anhydride to the lithium compound, formed *in situ*, leads exclusively to the undesired diketone **4**. Reverse addition, by which the lithium reagent is added slowly to phthalic anhydride, provides the acid **3** in about 30% yield. The mixture of **3-5** is easily separated without chromatography because of differences in acidity. The acids **3** and **5** are separated from the neutral ketone **4** by alkaline extraction. The insolubility of the diacid **5** in chloroform enables **3** and **5** to be separated by several digestions.

Elaboration of **3** to **10** by known procedures [6] provides the substrate for Friedel-Crafts cyclization [7], which occurred in 40% yield to give the desired ketone **11**. Phthalic anhydride recently has been found to react with 2-furanyllithium in a similar fashion [8]. Thus the procedure of Scheme I provides a facile synthesis of the title compound.

#### EXPERIMENTAL

Melting points were determined on an Electrothermal apparatus and are uncorrected. The <sup>1</sup>H nmr spectra were recorded at 60 MHz on a Varian EM 360 spectrometer. Infrared spectra were recorded on a Unicam SP 200G spectrophotometer. Tetrahydrofuran (THF) and diethyl ether were distilled from lithium aluminum hydride prior to use. Metalation reactions were carried out in a flame-dried apparatus under positive pressure of argon, which had been dried first by passing it through sulfuric acid and sodium hydroxide pellets. The molarity of butyllithium was determined by the method of Turner *et al.* [9]. Analysis (tlc) was performed on silica plates (Merck) in 9/1 chloroform/ethyl acetate (system A) or 4/1 chloroform/methanol (system B).

Scheme I



## 2-(3-Thienyl)benzoic Acid (3) and 1,2-Di(3-thienyl)benzene (4).

To a stirred solution of diethyl ether (100 ml) and 1.53 M butyllithium (65.3 ml) in hexane was added slowly at  $-70^{\circ}$  16.3 g (0.1 mole) of 3-bromothiophene in diethyl ether (50 ml). Stirring at  $-70^{\circ}$  was continued for 1 hour. The entire reaction mixture was transformed *via* a flex needle dropwise to a stirred solution of phthalic anhydride (14.8 g, 0.1 mole) in 100 ml of THF at  $-70^{\circ}$ . The mixture was stirred at this temperature for 2 hours, then allowed to come to room temperature, and finally stirred overnight. Water (100 ml) was added, and the reaction mixture was acidified to pH 2. The layers were separated, and the aqueous layer was extracted with diethyl ether ( $4 \times 50$  ml). The combined organic layers were washed with 30% aqueous sodium hydroxide solution ( $5 \times 50$  ml). The alkaline layer was decolorized with charcoal and washed twice with ether. The organic extracts were similarly decolorized and dried (sodium sulfate). The organic portions were filtered through Celite and concentrated by rotary evaporation. The residue was recrystallized from methanol to give 4, 4.5 g, 30%, mp  $110-112^{\circ}$ , Rf 0.71 (A); ir (potassium bromide):  $\nu$  1760 (C=O)  $\text{cm}^{-1}$ ;  $^1\text{H-nmr}$  (deuteriochloroform):  $\delta$  8.10-6.85 (m, 10H, aromatic). The alkaline layer was filtered through Celite, acidified with concentrated hydrochloric acid, diluted to 1.5 l with water, and cooled with an ice water bath. The resulting precipitate was filtered off, dried in air, and digested with hot chloroform ( $4 \times 50$  ml). The combined filtrates were concentrated by rotary evaporation until crystals began to appear. The solution was then left to stand in the refrigerator overnight. Phthalic acid 5 remained as the insoluble material, which was recrystallized from hot water (2 g, mp  $207-208^{\circ}$ ). The crystals from the chloroform digestions were filtered off, washed with petroleum ether, and dried in air: 8.8 g, 38%, mp  $162-164^{\circ}$ , Rf 0.42 (B); ir (potassium bromide):  $\nu$  3100 (COOH), 1720 (C=O), 1645 (C=O)  $\text{cm}^{-1}$ ;  $^1\text{H-nmr}$  (deuteriochloroform):  $\delta$  13.60-12.30 (s, 1H, COOH), 8.15-7.30 (m, 7H, aromatic).

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_8\text{O}_3\text{S}$ : C, 62.05; H, 3.47. Found: C, 62.10; H, 3.41.

## 2-(3-Thienyl)benzoic Acid (6).

The keto acid 3 (14.5 g, 0.062 mole) was stirred and heated to reflux for 24 hours in 1000 ml of ammonia with 39.3 g (0.6 mole) of zinc dust and 0.5 g of copper sulfate. During this period, 200 ml of ammonia was added every 4 hours. The reaction mixture was filtered while hot, acidified with concentrated hydrochloric acid to pH 1, diluted to 2 l with water, and cooled with running water. The resulting precipitate was filtered off and dried in air: 11.7 g, 87%, mp  $97-99^{\circ}$ , Rf 0.45 (B); ir (potassium bromide):  $\nu$  3000 (COOH), 1750 (C=O), 1700 (C=O)  $\text{cm}^{-1}$ ;  $^1\text{H-nmr}$  (deuteriochloroform):  $\delta$  11.15 (s, 1H, COOH), 8.20-7.72 (m, 7H, aromatic), 4.42 (s, 2H,  $\text{CH}_2$ ).

## 2-(3-Thienyl)benzyl Alcohol (7).

To a stirred suspension of lithium aluminum hydride (2.09 g, 0.055 mole) in diethyl ether (50 ml) was added the crude acid 6 in 100 ml of diethyl ether in a dropwise fashion. Stirring and heating was continued for 3 hours after completion of the addition. Water (100 ml) then was added very carefully, and the solution was acidified with 50% sulfuric acid. The layers were separated, and the aqueous portion was extracted with ether ( $5 \times 40$  ml). The combined organic extracts were washed with brine, dried (sodium sulfate), concentrated by rotary evaporation, and distilled under vacuum: 10 g, 89%, bp  $147-150^{\circ}$  (0.4 mm Hg),  $n_{\text{D}}^{20}$  1.6090, Rf 0.58 (B); ir (film):  $\nu$  3400 (OH)  $\text{cm}^{-1}$ ;  $^1\text{H-nmr}$  (deuteriochloroform):  $\delta$  7.30-6.35 (m, 7H, aromatic); 4.35 (s, 2H,  $\text{ArCH}_2$ ), 3.80 (s, 2H,  $\text{CH}_2\text{O}$ ), 3.30 (s, 1H, OH).

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_{12}\text{OS}$ : C, 70.54; H, 5.92. Found: C, 70.31; H, 6.00.

## 2-(3-Thienyl)benzyl Bromide (8).

The alcohol was treated with potassium tribromide to give the corres-

ponding bromide, 1.46 g, 55%, bp  $139-144^{\circ}$  (0.4 mm Hg),  $n_{\text{D}}^{20}$  1.6284; ir (film):  $\nu$  3050 (aromatic CH)  $\text{cm}^{-1}$ ;  $^1\text{H-nmr}$   $\delta$  7.31-6.60 (m, 7H, aromatic), 4.35 (2, 2H,  $\text{ArCH}_2$ ), 4.08 (s, 2H,  $\text{CH}_2\text{Br}$ ).

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_{11}\text{BrS}$ : C, 53.93; H, 4.15. Found: C, 53.75; H, 4.10.

## 3-(3-Thienyl)benzyl cyanide (9).

Treatment of the bromide (6.5 g, 0.024 mole) with sodium cyanide (1.66 g, 0.034 mole) gave the corresponding nitrile, 3 g, 58%, bp  $145-147^{\circ}$  (0.6 mm Hg),  $n_{\text{D}}^{20}$  1.5943, Rf 0.71 (A); ir (film):  $\nu$  2250 (CN)  $\text{cm}^{-1}$ ;  $^1\text{H-nmr}$  (carbon tetrachloride):  $\delta$  7.40-6.55 (m, 7H, aromatic), 3.89 (s, 2H,  $\text{ArCH}_2$ ), 3.40 (s, 2H,  $\text{CH}_2\text{CN}$ ).

*Anal.* Calcd. for  $\text{C}_{13}\text{H}_{11}\text{SN}$ : C, 73.20; H, 5.20. Found: C, 73.10; H, 5.15.

## 2-(3-Thienyl)phenylacetic acid (10).

Hydrolysis of the nitrile (3 g, 0.014 mole) with aqueous potassium cyanide (4.5 g in 6 ml) produced the acid, 2.57 g, 79%, mp  $86-87^{\circ}$ , Rf 0.59 (B); ir (potassium bromide):  $\nu$  2900 (COOH), 1710 (C=O)  $\text{cm}^{-1}$ ;  $^1\text{H-nmr}$  (deuteriochloroform):  $\delta$  10.50 (s, 1H, CO<sub>2</sub>H), 7.30-6.50 (m, 7H, aromatic), 4.01 (s, 2H,  $\text{ArCH}_2$ ), 3.67 (s, 2H,  $\text{CH}_2(\text{CO})$ ).

*Anal.* Calcd. for  $\text{C}_{13}\text{H}_{12}\text{O}_2\text{S}$ : C, 67.21; H, 5.21. Found: C, 67.10; H, 5.15.

9,10-Dihydro-4H-benzo[4,5]cyclohepta[1,2-*b*]thiophen-10-one (11).

To a stirred solution of the acid (1 g, 0.0043 mole) in 35 ml of dry benzene under argon at  $0-5^{\circ}$  was added 0.89 g (0.0043 mole) of phosphorus pentachloride in one portion. The temperature was allowed to rise slowly to room temperature, and the solution was refluxed for 3 hours. After the solution was cooled to  $0^{\circ}$ , stannic chloride (2.6 g, 0.01 mole) in 20 ml of benzene was added dropwise over 30 minutes. Stirring at  $0^{\circ}$  was continued for an additional 30 minutes, the cooling bath was removed, and stirring was continued for another 2.5 hours. The contents of the flask then was poured onto 100 g of ice and 30 ml of concentrated hydrochloric acid. The layers were separated, and the aqueous portion was extracted with chloroform ( $5 \times 30$  ml). The organic portions were separated and washed with water ( $2 \times 20$  ml). The combined organics were dried (sodium sulfate), concentrated by rotary evaporation, and crystallized from methanol/water and methanol/petroleum ether, 0.4 g, 44%, mp  $120-122^{\circ}$ , Rf 0.61 (A); ir (potassium bromide):  $\nu$  1655 (C=O)  $\text{cm}^{-1}$ ;  $^1\text{H-nmr}$  (deuteriochloroform):  $\delta$  7.16 (s, 4H, aromatic), 7.15 (ABq, 2H,  $J = 5.0$  Hz, thiophene CH), 4.16 (s, 2H,  $\text{ArCH}_2\text{Ar}$ ), 4.03 (s, 2H,  $\text{CH}_2\text{CO}$ ).

*Anal.* Calcd. for  $\text{C}_{13}\text{H}_{10}\text{OS}$ : C, 72.86; H, 4.70. Found: C, 73.03; H, 4.75.

## REFERENCES AND NOTES

- [1] E. Waldvogel, G. Schwarb, J.-M. Bastian and J.-P. Bourquin, *Helv. Chim. Acta*, **59**, 866 (1976), and lit cited therein.
- [2] D. W. H. MacDowell and J. C. Wisowaty, *J. Org. Chem.*, **36**, 3999 (1971).
- [3] The 2-thienoyl moiety can be easily introduced by Fridel-Crafts acylation of thiophene; see refs [2], [6], [7].
- [4] Y.-H. Lai, *Synthesis*, 586 (1981), and lit cited therein.
- [5] W. A. Lindley, D. W. H. MacDowell and J. L. Peterseon, *J. Org. Chem.*, **48**, 4419 (1983).
- [6] M. Rajsner, J. Metysova and M. Protiva, *Coll. Czech. Chem. Commun.*, **34**, 468 (1969).
- [7] W. A. Lindley and D. W. H. MacDowell, *J. Org. Chem.*, **47**, 705 (1982).
- [8] C. C. Lopes, R. S. C. Lopes, A. V. Pinto and P. R. R. Costa, *J. Heterocyclic Chem.*, **21**, 621 (1984).
- [9] R. R. Turner, A. G. Altanay and T. C. Cheng, *Anal. Chem.*, **42**, 1835 (1970).